Paper

LOW-DOSE RADIATION EPIDEMIOLOGY STUDIES: STATUS AND ISSUES

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Abstract—**Although the Japanese atomic bomb study and radiotherapy studies have clearly documented cancer risks from high-dose radiation exposures, radiation risk assessment groups have long recognized that protracted or low exposures to low-linear energy transfer radiations are key radiation protection concerns because these are far more common than high-exposure scenarios. Epidemiologic studies of human populations with low-dose or low dose-rate exposures are one approach to addressing those concerns. A number of large studies of radiation workers (Chernobyl clean-up workers, U.S. and Chinese radiological technologists, and the 15-country worker study) or of persons exposed to environmental radiation at moderate to low levels (residents near Techa River, Semipalatinsk, Chernobyl, or nuclear facilities) have been conducted. A variety of studies of medical radiation exposures (multiple-fluoroscopy, diagnostic ^{131}I, scatter radiation doses from radiotherapy, etc.) also are of interest. Key results from these studies are summarized and compared with risk estimates from the Japanese atomic bomb study. Ideally, one would like the low-dose and low dose-rate studies to guide radiation risk estimation regarding the shape of the dose-response curve, DDREF (dose and dose-rate effectiveness factor), and risk at low doses. However, the degree to which low-dose studies can do so is subject to various limitations, especially those pertaining to dosimetric uncertainties and limited statistical power. The identification of individuals who are particularly susceptible to radiation cancer induction also is of high interest in terms of occupational and medical radiation protection. Several examples of studies of radiation-related cancer susceptibility are discussed, but none thus far have clearly identified radiation-susceptible genotypes.**
Health Phys. 97(5):481–486; 2009

Key words: atomic bomb survivors; dose, low; epidemiology; National Council on Radiation Protection and Measurements

INTRODUCTION

THE RISK estimates used for current radiation protection standards have been based primarily upon the Japanese atomic bomb survivor experience because this study has a number of features that collectively make it extremely valuable: reasonably accurate individual dosimetry, a wide range of doses, a large population (120,000) of both sexes and all ages at exposure, a largely unselected population (e.g., not irradiated because of medical conditions or employment status), virtually complete ascertainment of mortality and cancer incidence, nearly 60 y of follow-up, and ancillary data on other disease risk factors (e.g., smoking) (Preston et al. 2007). Importantly, while the atomic bomb study is usually thought of as a "high-dose" study, in fact about 85% of the exposed cohort have estimated doses under 0.2 Gy and 80% under 0.1 Gy. Furthermore, a statistically significant dose-response relationship for solid cancers is seen even over the dose range of 0 to <0.15 Gy for both cancer incidence and mortality (Preston et al. 2003, 2007). There is mixed evidence regarding the shape of the dose-response curve: for leukemia there is substantial upward curvature at lower doses (Preston et al. 1994), for solid cancer mortality data there is a small amount of upward curvature (Preston et al. 2004), but for the solid cancer incidence there is no evidence of curvature (Preston et al. 2007).

However, two caveats have to be considered in using the atomic bomb study as a model for U.S. radiation protection purposes: the atomic bomb exposures were brief, single exposures rather than fractionated or protracted exposures, and disease incidence and mortality patterns differ between Japan and western countries, apparently reflecting differences in a mixture of various genetic, lifestyle, and environmental-exposure factors. As a result, certain assumptions need to be made to project risks from atomic bomb survivor studies to risks in western populations exposed to fractionated/protracted exposures.

In this review we will use the term "low dose" generically to refer to studies with low doses of low-linear energy transfer (low-LET) radiation and those with appreciable dose fractionation or protraction. Questions of interest are whether low-dose studies are informative in estimating radiation risk, and whether their risk estimates are compatible with those from the Japanese

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(*Manuscript accepted* 24 *April* 2009)

0017-9078/09/0

atomic bomb survivor study. A summary of the largest studies available (i.e., those with the greatest number of disease cases with exposure) will be presented, since these provide the best chance of reliably detecting and estimating low-dose risks.

RISK ESTIMATES IN LOW-DOSE STUDIES

First, leukemia risks will be examined, since leukemia is widely thought to be the most radiation-sensitive type of malignancy. Table 1 summarizes the risk estimates for the largest (post-natal) low-dose medical irradiation series. The first three entries in the table are cohort studies of irradiated populations, while the remainder are case-control studies performed in medical settings. It is notable that three of the studies showed a marginally statistically significant excess risk (Table 1), but if risks per unit dose could be calculated for these studies, the confidence limits would be very wide because of both the statistical and dosimetric uncertainties.

Table 2 shows the leukemia risks seen in the largest occupational or environmental low-dose radiation studies (but studies included in the 15-country radiation worker study were not included as separate entries). Three out of the six studies showed a statistically significant excess risk. Two of the three with a significant risk had the highest cumulative exposures, but the three also had more uncertainty in their dose estimates. Taken as a whole, the low-dose studies in Tables 1 and 2 are suggestive that there may be excess leukemia risk at low or protracted doses. However, the confidence intervals (CIs) on these studies are wide, so that they would not by themselves provide an adequate basis on which to estimate the magnitude of risk.

Table 1. Leukemia after low-dose medical radiation exposure.

	Mean dose (mGy)	No. of leukemias	RR or odds ratio (95% CI)
Arthrosis/spondylitis (Damber et al. 1995; Little 2001)	39	116	1.7 (<1–4.5)[a]
^{131}I for hyperthyroidism (Ron et al. 1998)	42	82	<1
TB fluoroscopic exams (Davis et al. 1989)	90	17	1.0 (0.5–1.8)
Diagnostic (Dx) x ray (Stewart et al. 1962)	?	160	1.3 (1.0–1.6)
Dx x ray (Gibson et al. 1972): 20+ x rays	?	69	1.5 (1.0–2.4)
Dx x ray (Preston-Martin et al. 1989): 10+ x rays	?	54	1.3 (1.0–1.7)
Dx x ray (Boice et al. 1991)	?	316	1.4 (0.9–2.2)
Dx radiation (Yuasa et al. 1997)	?	49	0.8 (0.5–1.2)

[a] Relative risk (RR) at 1 Gy. Others are RRs or odds ratios for the entire exposed group, irrespective of dose.

Table 2. Leukemia after protracted/fractionated occupational or environmental radiation exposure.

	Mean dose (mGy)	Number of leukemias	RR at 1 Gy (95% CI)
15-country worker study (Cardis et al. 2007)	19.4	196	2.9 (<1–9.5)
Los Alamos National Lab (Wiggs et al. 1994)	~16	44	~1
Portsmouth Naval Shipyard workers (Yiin et al. 2005)	20	34	12 (<1–40)
Chinese medical x-ray workers (Wang et al. 2002)	244	44	5.8 (~2.2–12)[a]
Techa River population (Ostroumova et al. 2006)	~400	60	4.6 (1.7–12)
Chernobyl fallout regions (Davis et al. 2006)[b]	~6.3	421	33 (10–85)

[a] An approximate confidence interval for this study was recalculated for the present paper because the original calculation failed to account for statistical variability in the comparison group.
[b] This is an ecological study, examining leukemia rates in regions according to estimates of regional fallout exposures.

Risk estimates for total solid cancers are shown in Table 3 for most of the largest low-dose studies for which there are whole-body radiation exposure estimates. About half of these studies showed a significantly increased solid cancer risk, suggesting there may be risk at low doses, but again do not provide a sufficient basis for risk estimation because of the uncertainties reflected in the wide CIs shown in the table, as well as the substantial uncertainties in dose estimates for several of the studies.

A comparison of two cohorts of persons with multiple fluoroscopic tuberculosis (TB) examinations with

Table 3. Total solid cancers after low-dose or protracted/fractionated exposures.

Study	Mean dose (mGy)	No. of cancers	RR at 1 Gy (95% CI)
Multiple fluoroscopic exams (Davis et al. 1989)	~250	429	0.8 (0.7–0.9)[a]
^{131}I for hyperthyroidism (Ron et al. 1998)	?	1742	1.0 (1.0–1.1)[a]
^{131}I for hyperthyroidism (Holm et al. 1991)	~60	1543	2.0 (1.1–2.9)
Chinese medical x-ray workers (Wang et al. 2002)	~240	836	1.8 (~1.5–2.1)[b]
15-country worker study (Cardis et al. 2007)	19.4	5024	2.0 (1.1–3.0)
Springfields U production plant (McGeoghegan and Binks 2000)	23	939	0.9[a]
Chernobyl clean-up workers (Ivanov 2007)	130	1370	1.3 (<1–2.2)
Techa River population (Krestinina et al. 2007)	~40	1846	2.0 (1.3–2.9)
Semipalatinsk fallout (Bauer et al. 2005)	634	889	1.8 (1.5–2.3)

[a] RR and CI for the mean dose in the study, rather than per Gy.
[b] An approximate CI for this study was recalculated for the present paper, because the original calculation failed to account for statistical variability in the comparison group.

the Japanese atomic bomb survivors affords an opportunity to examine risks from fractionated vs. single, brief exposures for breast and lung cancers. For lung cancer, the Canadian multiple-fluoroscopy cohort had a dose-response based excess relative risk estimate (ERR Gy^{-1}) of 0% (95% CI: −6, 7%) while the atomic bomb estimate with a comparable age/sex distribution was 60% (CI: 27, 99%) (Howe 1995). The null estimate of risk was congruent with the Massachusetts multiple-fluoroscopy study that found a standardized mortality ratio (SMR) for lung cancer that was nominally less than one (SMR = 0.8, CI: 0.6, 1.1) (Davis et al. 1989).

For breast cancer the results are different. For the Canadian multiple-fluoroscopy cohort the ERR Gy^{-1} was 90% (CI: 60, 140%) while for the atomic bomb survivor study it was 160% (CI: 40, 350%) (Howe and McLaughlin 1996). The CIs of these two estimates overlap considerably indicating no statistically significant difference, albeit the ERR Gy^{-1} is nominally somewhat lower in the fluoroscopy series. Little and Boice (2003) statistically compared the breast cancer risks in the Massachusetts multiple-fluoroscopy cohort and the atomic bomb survivor cohort, using a subset of the atomic bomb survivor cohort with a similar age distribution to the multiple-fluoroscopy series. A comparison of the two cohorts for radiation risk on the ERR scale showed that the atomic bomb risk was significantly greater [ratio of ERR coefficients: 2.5 (CI: 1.3, 6.0)]. However, they found that the difference appeared to be a function of the fact that the baseline breast cancer risks were appreciably lower in Japan than in the U.S. When they compared the excess absolute risks (EAR Gy^{-1}, i.e., number of excess cases $\times 10^{-4}$ person-year Gy) in the two populations, the atomic bomb to fluoroscopy ratio was only 0.9 (CI: 0.5, 1.7). Hence, on an EAR scale there was no difference in the risk estimates from highly-fractionated and single brief exposures. Dosimetry considerations could change this conclusion slightly (e.g., the relative biological effectiveness of low-energy x rays vs. gamma rays; possible inaccuracies in estimated fluoroscopy doses). Nevertheless, both fluoroscopy studies clearly demonstrate that fractionated doses, mostly on the order of 10 mGy per fraction (Sherman et al. 1978; Boice et al. 1978), increase breast cancer risk.

INDIVIDUAL SUSCEPTIBILITY TO BREAST CANCER FROM RADIATION EXPOSURE

A further area of potential importance regarding radiation low-dose risks is the possibility of susceptible subpopulations that are extra-sensitive to low doses of ionizing radiation. These susceptibilities could be a function of co-exposures (e.g., smoking and radiation in the case of lung cancer risk) or of genetic or physiologic status.

Several studies of radiation-related susceptibility to breast cancer will be summarized. It is well known epidemiologically that nulliparity and the age at first childbirth are important determinants of breast cancer risk (Zeleniuch-Jacquotte and Shore 2005), and this is an area of current biological investigation (Russo et al. 2008) Two studies have found evidence that first childbirth is also a modifier of radiation-related breast cancer risk (Boice and Stone 1978; Shore et al. 1980). For instance, Fig. 1 shows that women who were irradiated at the time of their first childbirth had a significantly greater radiation risk per unit dose than those irradiated at second or later childbirths, adjusting for age at exposure (Shore et al. 1980).

It is commonly observed that groups with high genetic risk of breast cancer (e.g., *BRCA1* or *BRCA2* mutations) or other cancers manifest a pattern of especially high risk at younger ages. Evidence from the Japanese atomic bomb study suggests there may be a subgroup with special genetic susceptibility to radiation-induced breast cancer at young ages, as shown in Fig. 2 (Land et al. 1993). The dose-dependent risk of breast cancer before the age of 35 among those irradiated before age 20 is greatly elevated compared to risk in later years, which suggests a gene x radiation-exposure interaction. A similar result was found among female Hodgkin disease patients given radiotherapy before age 20: before age 40 their relative risk (RR) was 63 (CI: 26, 128) whereas at ages 40–49 y it was 6.4 (CI: 1.7, 21) (van Leeuwen et al. 2000).

A few studies have tried to examine whether genetic susceptibility modifies the risk of breast cancer from

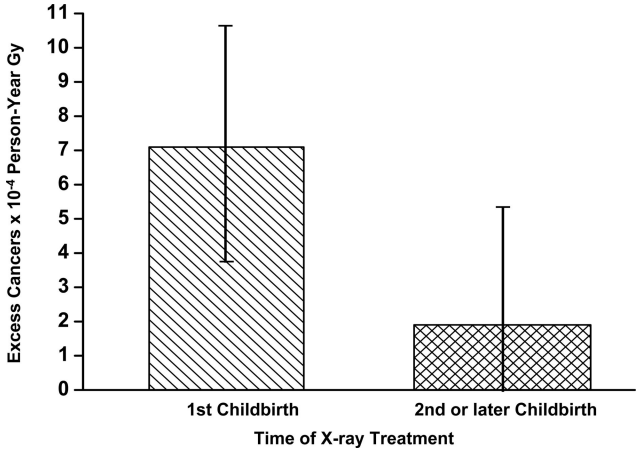

Fig. 1. X-ray treatment for acute postpartum mastitis: excess breast cancers from x-ray exposure associated with the first childbirth, or second or later childbirths (adjusted for age at exposure) (Adapted from Shore et al. 1980).

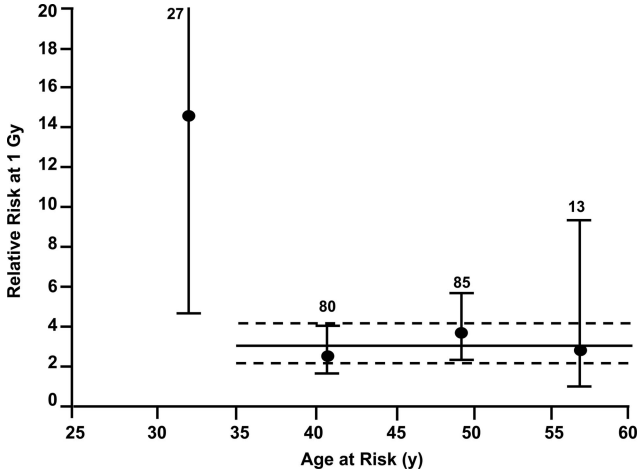

Fig. 2. Estimated relative risk (95% CI) of breast cancer at 1 Gy by age at risk among female atomic bomb survivors under 20 y of age at exposure. Numbers of cases are indicated. Horizontal lines represent the estimated risk and 95% CI for the three combined older attained-age groups (Land et al. 1993).

radiation at low dose levels. Andrieu et al. (2006) compared the reported history of screening/diagnostic chest x rays for those who did and did not develop breast cancer among a cohort of carriers of *BRCA1* or *BRCA2* mutations. They found an elevated risk overall for ever having had a chest x ray (RR = 1.5, CI: 1.1, 2.1). The risk was more pronounced for breast cancers occurring before age 40 y (RR = 2.0, CI: 1.3, 2.9) than for ≥40 y (RR = 1.3, CI: 0.8, 1.8). On the other hand, two other studies found no evidence that mammographic exams conferred breast cancer risk among *BRCA1/2* carriers (Narod et al. 2006; Goldfrank et al. 2006). A case-control study by Millikan et al. (2005) examined whether the radiation risk for breast cancer from mammography was modified by polymorphisms in several DNA repair genes, specifically, single-nucleotide polymorphisms (SNPs) in coding regions of the *XRCC2*, *XRCC3*, *NBS1* and *BRCA2* genes. They reported that, while the SNPs individually did not significantly modify radiation risk, those who had multiple SNP variants showed a statistically significant trend in risk with respect to number of mammograms. However, a cautionary note: all of the aforementioned radiation susceptibility studies relied on retrospective reporting regarding radiation exposure history after the breast cancers had occurred, so they may have been subject to recall bias. Studies among the U.S. radiologic technologist cohort found evidence that polymorphisms in the *IL1A*, *WRN*, *BRCA1*, *PRKDC* and *H19* genes modified the radiation risk of breast cancer, but since these were the only associations out of a large number of genes and statistical tests, they require replication to substantiate the findings (Sigurdson et al. 2007; Bhatti et al. 2008a and b). A carefully designed study found that breast cancer cases with the *CHEK2*1100delC* mutation and radiotherapy had a nonsignificant suggestion that the combination of the two increased the risk of a second breast cancer (RR = 2.6, 95% CI: 0.8–9) (Mellemkjaer et al. 2008).

To summarize, we currently know little about how genetic variation may modify radiation risk and no idea of what impact, if any, this may have on low-dose radiation risk assessment or on whether radiation standards should be modified to protect the most susceptible. Till now there is only a small literature on genetic susceptibility and radiation and many of the existing studies are too small to provide more than suggestions of possible gene x radiation-exposure interactions, but it is anticipated that this literature will increase substantially in the next several years to begin to address the issue.

CONCLUSION

In conclusion, the ultimate goal for radiation epidemiology is a body of data based on low-dose, protracted radiation exposures with accurate individual doses, information on potential confounding variables, and sufficient statistical precision to estimate low-dose risks with very little uncertainty. Unfortunately, estimating low-dose risks with little uncertainty is unlikely to occur, as low-dose studies nearly always have inadequate statistical power and precision. This means that low-dose studies are very susceptible to false-negative and magnified false-positive results (Land 1980). Nevertheless, low-dose studies broadly have utility to confirm or disconfirm the risks extrapolated from higher doses. The summary of studies presented here tends to confirm that some leukemia and solid cancer risk is likely from low doses or fractionated or protracted exposures, although the data from the low-dose studies are too uncertain and variable to meaningfully quantify the degree of risk.

Acknowledgments—The clerical and technical assistance of Ritsko Shibukawa and Mahoko Fujiwara is gratefully acknowledged. Support was provided by the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan, which is a private, non-profit foundation funded by the Japanese Ministry of Health, Labor and Welfare (MHLW) and the U.S. Department of Energy (DOE), the latter partly through the U.S. National Academy of Sciences. The conclusions expressed herein are solely the views of the author and do not imply endorsement by RERF or its sponsoring agencies.

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